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minimal. Niacin treatment during the morning and evening resulted in decreased T_a and MAP and increased \dot{T}_{sk} , SkBF, FBF, heart rate, and CVC ($p < 0.05$). Peak HR at 1800 h was $25 \text{ b} \cdot \text{min}^{-1}$ higher than at 0800 h ($p < 0.05$). MAP decreased an average of 12 Torr in the morning experiments and nearly 16 Torr in the evening experiments. Two of the four subjects experienced severe hypotension after niacin treatment at 1800 h. A diurnal factor, presumably influencing the responsiveness of the cardiovascular system, may play a role in the hypotensive effect of niacin at night. These data suggest that niacin ingestion at night may have more adverse cardiovascular effects than in the morning.



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NIACIN INGESTED AT NIGHT CAUSES SEVERE HYPOTENSION

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Abstract

The purpose of the study was to determine whether or not the cardiovascular responses to niacin ingestion was affected by the time of day. Four healthy subjects were studied during rest while in a seated posture in a moderately warm environment ($T_a = 30^\circ\text{C}$, $rh = 23\%$) at 0800 h and again between 1800 and 2100 h. The evening experiments were done approximately 4 h before each subject normally went to bed. Esophageal temperature (T_{es}), mean weighted skin temperature (\bar{T}_{sk}), forearm blood flow (FBF, venous occlusion plethysmography), skin blood flow (SkBF, laser doppler velocimetry), mean arterial pressure (MAP) and heart rate (HR) were measured twice each minute. After instrumentation, a 15 minute control period was initiated. T_{es} and \bar{T}_{sk} were 0.4 ($p \leq 0.05$) and 0.6°C higher at 1800 h than 0800 h. Skin blood flow was 47% higher ($p \leq 0.05$) and cutaneous vascular conductance (CVC) was 43% greater ($p \leq 0.05$) at 1800 h. Five mg niacin per kg body weight was ingested after the control period. The onset time for niacin effects showed individual variability, Therefore, the data were compared during pretreatment, the time of maximal vasodilation, and when T_{es} was minimal. Niacin treatment during the morning and evening resulted in decreased T_{es} and MAP and increased \bar{T}_{sk} , SkBF, FBF, heart rate, and CVC ($p \leq 0.05$). Peak HR at 1800 h was $25 \text{ b} \cdot \text{min}^{-1}$ higher than at 0800 h ($p \leq 0.05$). MAP decreased an average of 12 Torr in the morning experiments and nearly 16 Torr in the evening experiments. Two of the four subjects experienced severe hypotension after niacin treatment at 1800 h. A diurnal factor, presumably influencing the responsiveness of the cardiovascular system, may play a role in the hypotensive effect of niacin at night. These data suggest that niacin ingestion at night may have more adverse cardiovascular effects than in the morning.

Long term administration of niacin alone¹ or in combination with other drugs^{2,4} reduces hypercholesterolemia, the incidence of nonfatal myocardial infarction,^{2,3} and the progression of coronary atherosclerosis¹. However, niacin has been associated with side effects^{2,4,5}. Goldstein⁶ recently addressed the potential problems which might occur as a larger percentage of the general public becomes aware that this vitamin can dramatically decrease high blood cholesterol levels and that it is available without prescription. In particular, he mentioned that the popular book by Kowalski⁷ may persuade a segment of readers to use large doses of niacin as a supplement to a restricted fat and cholesterol diet. This possibility remains viable because Kowalski devoted a chapter of the latest edition of his book⁷ to niacin therapy, although he cautions that niacin should be used only after consulting a physician. As Goldstein⁶ pointed out, it is likely that some patients may begin taking niacin to combat high blood cholesterol without being supervised by a physician. The many undesirable side effects of niacin^{2,7,8} which are known to physicians are not necessarily common knowledge to the general public.

Recently,⁹ the thermoregulatory responses of human volunteers to a smaller dose (300-400 mg) of niacin than clinically therapeutic (1-7 g) was investigated. In addition to the well documented^{1,7,8,10} cutaneous vasodilation, a marked hypotensive effect of niacin was reported. The cutaneous vasodilation was sufficient to decrease core temperature and increase skin temperature.⁹ In continuing the investigation of this same dose of niacin as a vasodilatory agent, we observed that niacin affects the circulatory system differently at night than in the morning which could result in serious consequences to unwary patients. This report describes the magnitude of the hypotensive response to niacin given at two times of day in resting, healthy, young subjects. The diurnal facet of the study was terminated after two of the four subjects suffered severe hypotension, but the data collected

is of interest to the medical community given the importance of controlling high blood cholesterol and the role that niacin might play as a preventive measure against development of atherosclerotic heart disease.

Methods

Four subjects (three males and one female) volunteered to serve as subjects after they were verbally apprised of the nature and risks of the study. The physical characteristics (mean \pm standard deviation) of the subjects are as follows: age: 29 (± 5) years; height: 172 (± 5) cm; weight: 69.2 (± 3.6) kg; and body surface area: 1.79 (± 0.05) m².

The subjects were completely familiar with all laboratory techniques before the study began. Subjects were studied during rest in a moderately warm environment ($T_a = 30 (\pm 1)^\circ\text{C}$; $P_a = 1 (\pm 0.1)$ kPa) while in a seated posture at two different times of day. One experiment was done in the morning at 0800 h and the second experiment was done in the evening between 1800 and 2100 h. The experimental protocol was the same for both experiments. The evening experiments were designed so that the subject was studied approximately 4 h before he/she normally went to sleep at night. The woman was studied in the follicular phase of her menstrual cycle.

Each subject reported to the environmental test chamber after fasting at least 6 h before the experiment. A copper-constantan thermocouple encapsulated in a catheter was swallowed for the measurement of esophageal temperature (T_{es}) and skin thermocouples (copper-constantan) were attached to the forehead, chest, back, upper arm, lower arm, hand, thigh and calf. The location of the esophageal thermocouple was at heart level and was verified by varying the depth of the thermocouple until the highest temperature was recorded. The thermocouple was inserted at the same depth in the esophagus for both experiments. Venous occlusion plethysmography was used to measure forearm blood flow

(FBF),¹⁴ laser doppler velocimetry was used to measure skin blood flow (SkBF)¹⁷ and an automatic blood pressure monitor (Accutorr) was used to determine mean arterial pressure and heart rate.

After all instruments were attached to the subject, a 15 min control period was initiated. During this period, esophageal and skin temperatures, forearm blood flow and skin blood flow were measured every 0.5 min, and blood pressure and heart rate were measured every 5 min. Five mg niacin per kg body weight was ingested by each subject after the control period. Data were collected after niacin ingestion as was done for the control period, except blood pressure and heart rate were measured every min.

Mean skin temperature (\bar{T}_{sk}) was calculated as a weighted average of the local skin temperature of the eight sites measured.¹⁴ Mean body temperature (\bar{T}_b) was calculated from the equation:

$$\bar{T}_b = 0.8 (T_{re}) + 0.2 (\bar{T}_{sk}), \quad ^\circ\text{C}$$

Cutaneous vascular conductance (CVC) was calculated from MAP and SkBF.²⁰

The diurnal variation in pre-treatment T_{re} , \bar{T}_{sk} , MAP, HR, SkBF, FBF and CVC was analyzed by a one way analysis of variance with repeated measures. Other data were analyzed by a two way analysis of variance with repeated measures, with the factors being experimental time (pretreatment (A1), niacin treatment when FBF was at a peak (A2) and niacin treatment when T_{re} was minimal (A3)) and time of day (0800 (B1) and 1800 (B2) h). Tukey's tests of critical differences were performed when appropriate.

Results

Table 1 shows the pretreatment means in esophageal temperature, mean skin temperature, skin blood flow, forearm blood flow, mean arterial pressure, heart rate and cutaneous vascular conductance at two times of day. T_{re} and \bar{T}_{sk} increased 0.4 ($p < 0.05$)

and 0.6°C respectively at 1800 h compared to 0800 h. In the evening experiment skin blood flow increased 47% ($p < 0.05$) compared to the morning experiment. Although forearm blood flow was 115% greater in the evening, this difference was not statistically significant. Both heart rate and mean arterial pressure were greater in the evening than in the morning, but this difference was not statistically significant. CVC was significantly increased in the evening and was 43% greater ($p < 0.05$) than in the morning.

The onset time for niacin effects was not significantly different at the two times of day and averaged $18.6 (\pm 4.8)$ min at 0800 h and $14.5 (\pm 3.3)$ min at 1800 h. Because of the individual variability in onset of niacin responses the experimental data were compared statistically during pretreatment, at the time of maximal cutaneous vasodilation in the forearm and when T_{sk} was minimal or when the individual response was maximal.

The time course of the physiologic responses to niacin at the two times of day is shown for one subject in Figs. 1-3. T_{sk} and \bar{T}_{sk} are shown in Fig. 1. The rapid change in T_{sk} between 15 and 20 min of the experiments was due to the cooling effect of drinking water (30-50 ml) after taking the drug. \bar{T}_{sk} increased dramatically at 0800 h after the drug was taken, but at 1800 h the relative change in \bar{T}_{sk} was not as great even though the absolute mean skin temperature was nearly the same as in the morning. During the experiment at 1800 h the subject felt light-headed and dizzy at about 60 min (45 min after taking the drug). At 62 min the venous occlusion plethysmographic measurements were discontinued (Fig. 2) and the subject's body position was changed from a seated to a supine posture. All other data collection continued. The change in posture was accompanied by a transient increase in T_{sk} . SkBF also increased dramatically when the subject assumed the supine posture. Fig. 3 shows the response of mean arterial pressure and heart rate during the two experiments.

supine posture. All other data collection continued. The change in posture was accompanied by a transient increase in T_{re} . SkBF also increased dramatically when the subject assumed the supine posture. Fig. 3 shows the response of mean arterial pressure and heart rate during the two experiments.

Subject 2 experienced dizziness and tunnel vision which was severe enough to warrant termination of the experiment. His mean arterial pressure fell to 59 Torr by 26.5 min after niacin ingestion before he was placed in a supine position and a cold towel was placed on his neck. Fig. 4 shows the blood pressure and heart rate data for this subject. Subject 2 remained supine for approximately 40 min. SkBF had increased by 436% to 150 mV from a pretreatment value of 28 mV before severe hypotension occurred and FBF responded similarly. Resting SkBF and FBF were greatly increased at 1800 h compared to 0800 h in this subject as was CVC.

Table 2 compares the average responses of the subjects at three different times during the two experiments. The mean data show responses to niacin treatment similar to those shown for Subject 1 (Figs. 1-3). Esophageal temperature decreased by 0.6°C at 0800 h and 0.5°C at 1800 h after niacin treatment and \bar{T}_{re} increased by 0.7 and 0.5°C at 0800 and 1800 h respectively. Mean body temperature decreased 0.3°C in both experiments. SkBF increased by about 500% after niacin treatment during the 0800 h experiment, but during the 1800 h experiment only increased 407%. However, the absolute SkBF was higher at 1800 h than at 0800 h. Similarly, the relative increase in FBF was greater in the morning than in the evening, but the absolute FBF was greater at 1800 h. Mean arterial pressure decreased by about 12 Torr in the morning experiment after niacin treatment and nearly 16 Torr in the evening experiment. The peak heart rate was greater after niacin

at 1800 h than at 0800 h.

Comment

The evidence²⁴ that niacin therapy alone or in combination with other drugs is an effective method of reducing the incidence of nonfatal myocardial infarction, progression of atherosclerosis, and the ratio of total cholesterol/high density lipoprotein cholesterol and increasing high-density lipoprotein cholesterol is worthy of consideration. However, physicians must weigh both the beneficial and undesirable effects of niacin before any decision regarding niacin therapy can be made. The results from the current study suggest that there is an additional troublesome side effect of niacin administered per os to healthy volunteers in the evening. In addition to the marked cutaneous vasodilation and decreased mean arterial pressure which also occurred at 0800 h (Table 2), niacin treatment at 1800 h evoked hypotension severe enough to cause dizziness in two of four subjects.

Mean arterial pressure decreased after niacin treatment by 14.8% at 0800 h and decreased more (19%) in the experiment at 1800 h ($B1 < B2$, $p = 0.263$; $A \times B$ interaction = 0.060, Table 2). We could not show statistically that the severity of hypotension was more pronounced during the experiment at 1800 h than at 0800 h because the investigators and medical staff had to act promptly to counteract the hypotensive effect of niacin in two subjects which hampered data collection. The counteractive measures were to place a cold compress against the neck of the subjects and to change them from seated to a supine position. Also, the feet of one subject (Subject 2) were raised above the level of the heart. These counteractive measures effectively increased mean arterial pressure (Figs. 3 and 4). However, because these experiments took place in a research laboratory and not in a clinical situation, we decided to report the results on only four subjects rather than continue the study. Also, we were not willing to delay the counteractive measures to the

hypotensive episodes during the evening experiments in order to completely evaluate the magnitude of the response. Because the subject number was small ($n = 4$), the probability of committing a type II error is relatively high, and the power of the test is reduced.

The mean arterial pressure response in the other two subjects in the experiment at 1800 h was also greater than at 0800 h, although they did not experience symptoms of extreme hypotension. In one of these subjects the magnitude of the SkBF response to niacin treatment was about equal in the two experiments, although SkBF at 1800 h was greater than at 0800 h in the other subject. Subjects 3 and 4 tolerated the more pronounced decrease in mean arterial blood pressure after niacin treatment at 1800 h compared to 0800 h, and peak heart rate with niacin treatment for the two subjects respectively was 17 and 4 beats \cdot min $^{-1}$ higher at 1800 h than at 0800 h. On the other hand, the peak heart rates of Subjects 1 and 2 after niacin treatment was 45 and 32 beats \cdot min $^{-1}$ higher, respectively, in the evening than in the morning.

The physiologic explanation for the more severe decrease in mean arterial pressure during niacin treatment at 1800 h compared to 0800 h is not yet clear. It appears that there is diurnal change in the responsiveness of the cardiovascular system which increases the hypotensive effect of niacin. This diurnal event could be related to the increased SkBF at 1800 h compared to 0800 h (Table 1; $p = 0.024$); modification of skin blood flow is an integral part of the circadian rhythm in the control of thermoregulation.²¹ The increased CVC before niacin treatment at 1800 h compared to 0800 h is another indication that cardiovascular responsiveness may be different at the two times of day.

There is some evidence that the vasodilatory mechanism of action of nicotinic acid is via a prostanoid intermediary. Kaijser *et al.*²² reported that indomethacin significantly reduced the forearm blood flow response to nicotinic acid. Another study showed that

indomethacin was more effective than benorylate, a less potent prostaglandin synthetase inhibitor, in reducing the skin temperature response to nicotinic acid.²² It has also been reported that prostaglandin excretion was increased two days after initiation of niacin treatment in hyperlipidemic women,²³ although prostaglandin excretion was at control level again after 28 days of treatment. It was noted that flushing in response to the drug had also abated by that time. Prostacyclin (PGI_2), which has direct action on vascular smooth muscle cells, has been postulated to be the vasodilatory intermediary of nicotinic acid.²⁴ The effects of infusion of PGI_2 into human subjects include cutaneous vasodilation and increased skin temperature²⁵ and are similar to the effects of nicotinic acid ingestion. Infusion of a higher dose of PGI_2 in two subjects caused systolic and diastolic blood pressure to fall.²⁶ However, a more recent report²⁷ indicated that PGD_2 was the more likely prostaglandin mediator of the vasodilatory action because a metabolite of PGD_2 , 9α - 11β - PGF_2 , increased in the plasma of volunteers and reached maximal concentration around the time of maximal flushing after ingestion of 500 mg of nicotinic acid. The apparent diurnal variation of the effect of niacin on cardiovascular responses may be another example of the effects of biological rhythms on the practice of medicine²⁸ and could be due to diurnal variation in: 1) the synthesis of the prostanoid with niacin treatment so there is a greater amount of the vasodilatory compound to act on available smooth muscle receptors; 2) the affinity of the prostanoid for the vascular smooth muscle receptor;²⁹ 3) prostanoid receptor number, signal processing or placement; 4) the clearance of the vasodilatory component; and 5) a vasoconstrictor factor which modulates the prostanoid vasodilatory action. Blood glucose and free fatty acid concentration were not determined in this study so it is unknown whether nicotinic acid treatment resulted in a variable metabolic response at the two times of day.

Data from the current study also need to be considered in the context of a recent proposal to investigate the use of niacin therapy in the treatment of heatstroke.^{2,30} Niacin treatment in healthy, inactive subjects decreased mean arterial pressure dramatically at both times of day studied and could result in dire consequences if mean arterial pressure were already compromised as it is in heatstroke.

The method of niacin treatment used in the current study was different than that used in the clinical situation. First, the human volunteers were healthy and ingested the drug after fasting at least 6 h, while in the clinical situation, niacin is usually taken with meals. Also, aspirin or some other prostaglandin synthetase inhibitor is combined with niacin therapy to moderate the degree of cutaneous flushing in the clinical situation. The dose of niacin in the current study was $5 \text{ mg} \cdot \text{kg}^{-1}$ or between 300 and 400 mg. Anywhere from 1-7 g might be given daily in the clinical situation. Also, the environmental conditions of the test chamber simulated typical exposures of a summer day (30°C) with 29% relative humidity. The \bar{T}_{sk} averaged 33.9 and 34.5°C at 0800 and 1800 h, respectively. It may be that the cutaneous vasodilatory response to niacin would be less when ambient temperature and \bar{T}_{sk} were less. In addition, the subjects in the current investigation remained in the seated posture throughout the experiment. Some patients may remain in a seated posture for an hour or longer in certain jobs, while driving a vehicle, or even while viewing television or a movie. In other situations, patients will be fairly active and exercise will increase MAP and decrease the probability of an hypotensive episode. Finally, the drug was purposefully given to subjects in the current investigation when it was anticipated that the circadian rhythm in core temperature was near its peak.

It may be that the severe hypotensive episodes which we report in the current study are only possible if a patient takes niacin in a warm environment while fasting and when

he or she is not active. Nevertheless, the cutaneous vasodilatory effect of niacin and the resultant decreased mean arterial pressure is an indication that niacin therapy presents a potential danger about which physicians should be informed. Also, the results of this study demonstrate that even more attention should be given to the potential for the public, in their zeal to reduce high blood cholesterol, to take niacin without consulting a physician.

Table 1. Mean (\pm SD) pretreatment data at 0800 h and 1800 h.

<u>Variable</u>	<u>0800 h</u>	<u>1800 h</u>	<u>p Value</u>
T_{re} (°C)	36.6 (0.3)	37.0 (0.2)	0.027
\bar{T}_{sk} (°C)	33.9 (0.3)	34.5 (0.4)	0.093
SkBF (mV)	23.1 (8.0)	33.9 (11.5)	0.024
FBF (ml•100 ml ⁻¹ •min ⁻¹)	2.6 (1.2)	5.6 (3.9)	0.300
HR (beats•min ⁻¹)	52 (8)	57 (7)	0.122
MAP (Torr) [kPa]	85 (3) [10.80]	89 (7) [11.20]	0.138
CVC (mV•Torr ⁻¹)	28.5 (9.5)	40.7 (12.9)	0.010

Table 2. Individual data were analyzed by two-way analysis of variance with repeated measures. Factor A was experimental time and Factor B was time of day. Data presented are means (\pm SD) before niacin treatment (A1), after peak response of FBF to niacin (A2), and after maximal response of T_{re} to niacin (A3) during the 0800 h (B1) and 1800 h (B2) experiments.

	0800 h(B1)			1800 h(B2)		
	Pre(A1)	Niacin(A2) (peak FBF)	Niacin(A3) (min T _a)	Pre(A1)	Niacin(A2) (peak FBF)	Niacin(A3) (min T _a)
T _a (°C)	36.6 (0.3)	36.2 (0.3)	36.0 (0.4)	37.0 (0.2)	36.6 (0.2)	36.5 (0.2)
	A1>A2>A3 p = 0.0001; B1<B2 p = 0.018					
T _a	33.9 (0.3)	34.5 (0.3)	34.6 (0.4)	34.5 (0.4)	34.9 (0.7)	35.0 (0.6)
	A1<A2<A3 p = 0.0004; B1<B2 p = 0.289					
T _a (°C)	36.1 (0.3)	35.9 (0.3)	35.8 (0.3)	36.5 (0.2)	36.3 (0.3)	36.2 (0.3)
	A1>A2>A3 p = 0.0005; B1<B2 p = 0.027					
SkBF (mV)	23.1 (8.0)	123.0 (67.0)	138.0 (50.7)	33.9 (11.5)	172.0 (65.7)	154.8 (76.9)
	A1<A2, A1<A3 p = 0.0025; B1<B2 p = 0.278					
FBF (ml•100 ml ⁻¹ •min ⁻¹)	2.6 (1.2)	17.6 (4.3)	10.9 (3.1)	5.6 (3.9)	21.2 (8.1)	11.9 (5.5)
	A1<A2, A1<A3, A2>A3 p = 0.0006					

	0800 h(B1)			1800 h(B2)		
	Pre(A1)	Niacin(A2) (peak FBF)	Niacin(A3) (min T _a)	Pre(A1)	Niacin(A2) (peak FBF)	Niacin(A3) (min T _a)
MAP (Torr)	81 (3)	72 (4)	69 (2)	84 (7)	81 (6)	68 (9)
[kPa]	[10.80]	[9.60]	[9.20]	[11.20]	[10.80]	[9.07]
	$A_1 > A_2 > A_3 \quad p = 0.0000; B_1 < B_2 \quad p = 0.263; A \times B \quad p = 0.060$					
HR (b·min ⁻¹)	52 (8)	60 (6)	66 (6)	57 (7)	72 (17)	91 (22)
	$A_1 < A_2, A_1 < A_3 \quad p = 0.0041; B_1 < B_2 \quad p = 0.043$					
CVC (mV·Torr ⁻¹)	28.5 (9.4)	173.2 (97.2)	182.2 (76.4)	40.7 (12.9)	217.2 (91.2)	233.7 (81.2)
	$A_1 < A_2, A_1 < A_3 \quad p = 0.0026; B_1 < B_2 \quad p = 0.184$					

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The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy, or decision, unless so designated by other official documentation. Human subjects participated in these studies after giving their informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

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Figure 1. Esophageal and mean skin temperatures as a function of experimental time at two times of day (Subject 1). The subject swallowed 300 mg niacin with a drink of water at 15 min. The drink transiently cooled the esophageal thermocouple.

Fig. 1

SUBJECT 1

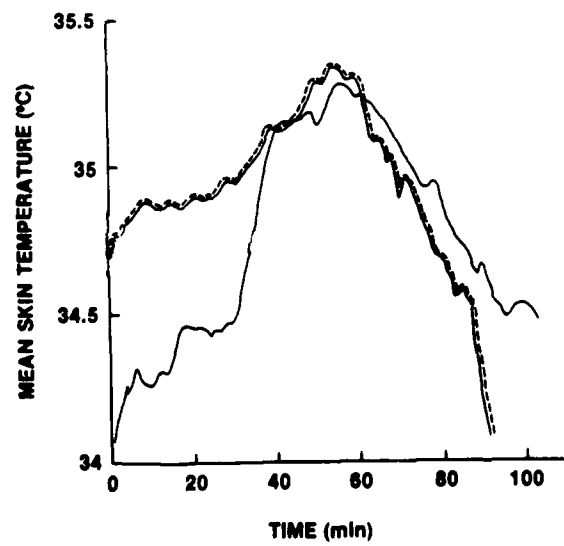
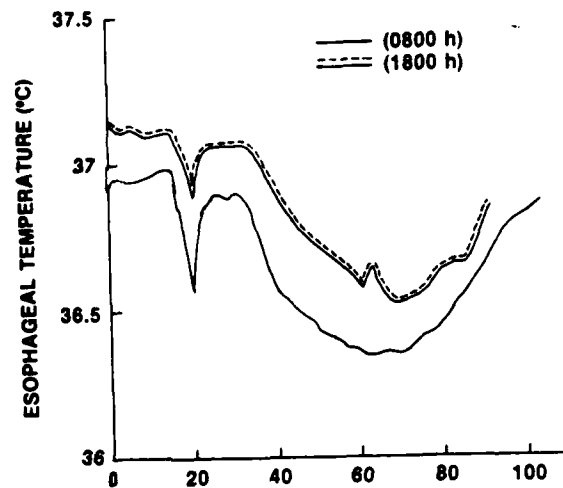


Figure 2. Laser doppler flow as an index of skin blood flow and forearm blood flow as a function of experimental time at two times of day (Subject 1). The subject swallowed 300 mg niacin with a drink of water at 15 min.

Fig. 2

SUBJECT 1

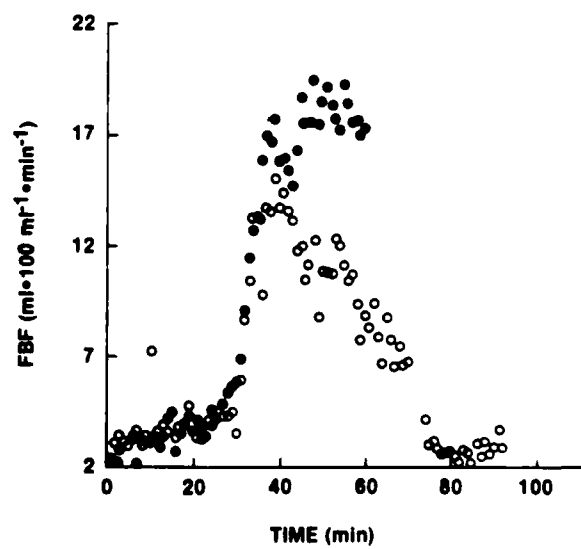
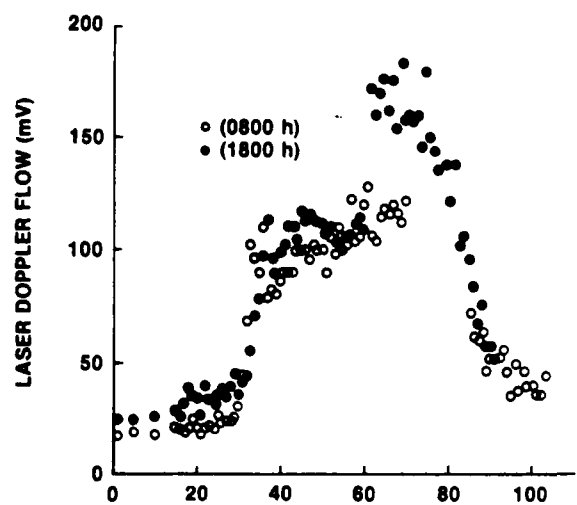


Figure 3. Mean arterial pressure (MAP) and heart rate as a function of experimental time at two times of day (Subject 1). The subject swallowed 300 mg niacin with a drink of water at 15 min.

Fig. 3

SUBJECT 1

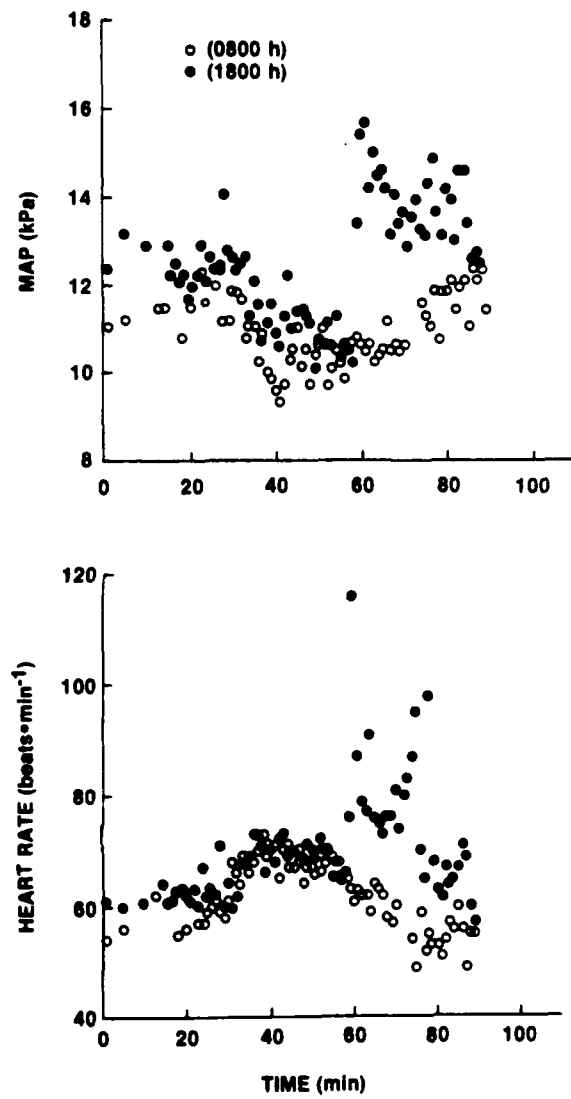


Figure 4. Systolic and diastolic blood pressure and heart rate as function of experimental time at two times of day (Subject 2). The subject swallowed 400 mg niacin with a drink of water at 15 min.

Fig. 4

